REMARKS

Information Disclosure Statement

On the copy of the June 12, 2005 Form PTO/SB/08A that was enclosed with the May 28, 2009 Office Action, a line was drawn through JP 2726672 and the following notation were in the left column thereto: "not considered"; "no translation".

JP 2726672 is described in the second full paragraph on page 2 of the present specification. Moreover, USP 4,952,581 is a related family member of JP 2726672. USP 4,952,581 is of record in this application.

It is respectfully submitted that based on the preceding paragraph, a concise statement of relevance has been provided for JP 2726672.

The Examiner is therefore respectfully requested to provide a copy of the June 12, 2005 Form PTO/SB/08A with the Examiner's initials next to each cited publication, including JP 2726672, to indicate that JP 2726672 was considered and made or record.

Claim

New claim 13 recites a feature of claim 4.

Obviousness Rejection Under 35 USC 103

Claims 1 to 4 were rejected under 35 USC 103 as being unpatentable over Azuma et al. (WO 00/09162) (USP 6,673,812) for the reasons set forth in item no. 8 on pages 3 to 4 of the May 28, 2009 Office Action.

It was admitted in the previous Office Action of May 28, 2009 that Azuma et al. do not expressly teach a composition comprising the combination of a Rho kinase inhibitor and a beta-blocker.

The rejection is on the ground that it would be obvious for one of skill in the art to combine two known drugs for the same purpose to form a combination for that purpose with a reasonable expectation of success (see page 3, lines 18 to 20 of the May 28, 2009 Office Action).

Applicants disagree with the rejection for the following reasons.

It was stated in the sentence bridging pages 3 and 4 of the May 28, 2009 Office Action that Azuma et al. teach a combination therapy since Azuma et al. describe that a Rho kinase inhibitor compound can be used alone or in combination with several kinds of compounds (column 9, lines 3 to 5 of Azuma et al.). However, Azuma et al. do not teach which type of glaucoma agent can be complimented and/or enhanced by a Rho kinase inhibitor. Moreover, Azuma et al. do not teach or suggest which Rho kinase inhibitor is preferable for such combination.

In contrast to Azuma et al., the present inventors discovered that a Rho kinase inhibitor can compliment and/or enhance the ocular hypotensive effect of a β-blocker, which is known as a glaucoma agent. Further, the present inventors also discovered after intense studies that among many Rho kinase inhibitors (R)-(+)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)benzamide (also known as "Y-39983") is especially preferable for combination with a β-blocker for glaucoma treatment (see applicants' claim 1).

As an evidence that Y-39983 is more preferable to be combined with a β-blocker than other Rho kinase inhibitors, submitted herewith is a DECLARATION UNDER 37 CFR 1.132 of Masakazu HATANO dated July 21, 2009 (hereinafter referred to as the "HITANO DECLARATION"). The HATANO DECLARATION shows a study of the effect on intraocular pressure (IOP) when the combination

of a Rho kinase inhibitor other than Y-39983, 1-(5-isoquinolinesulfonyl)-homopiperazine (also known as "HA1077"), and timolol, which is a representative β-blocker compound, was instilled to normotensive rabbits. The results of such study are set forth in Fig. A and Table A of the HITANO DECLARATION, which are reproduced as follows.

Fig. A Effect of topical adminstration of HA1077 and timolol in combination on IOP in ocular normotensive rabbits

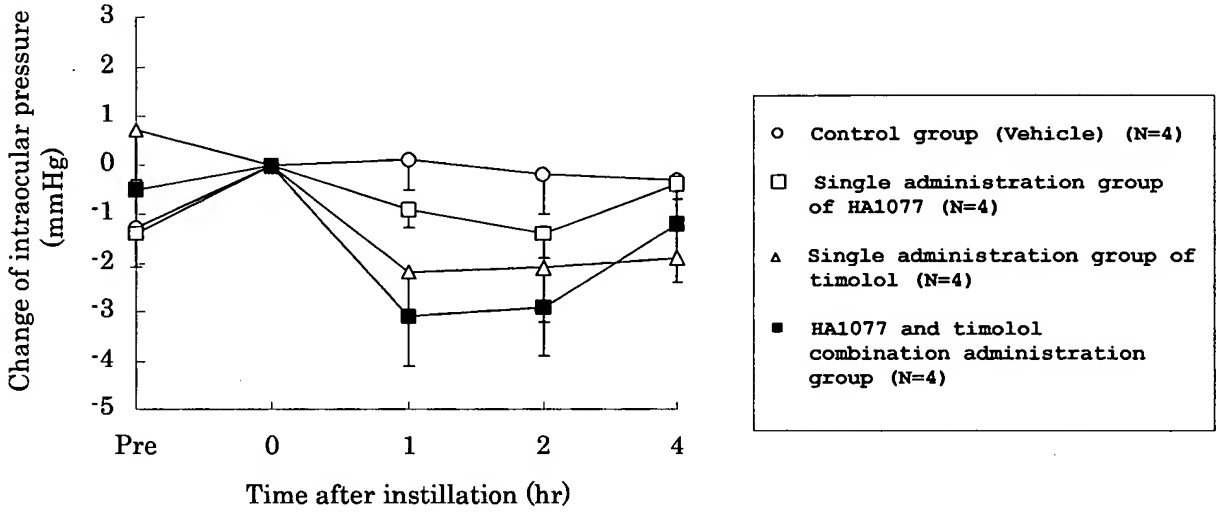
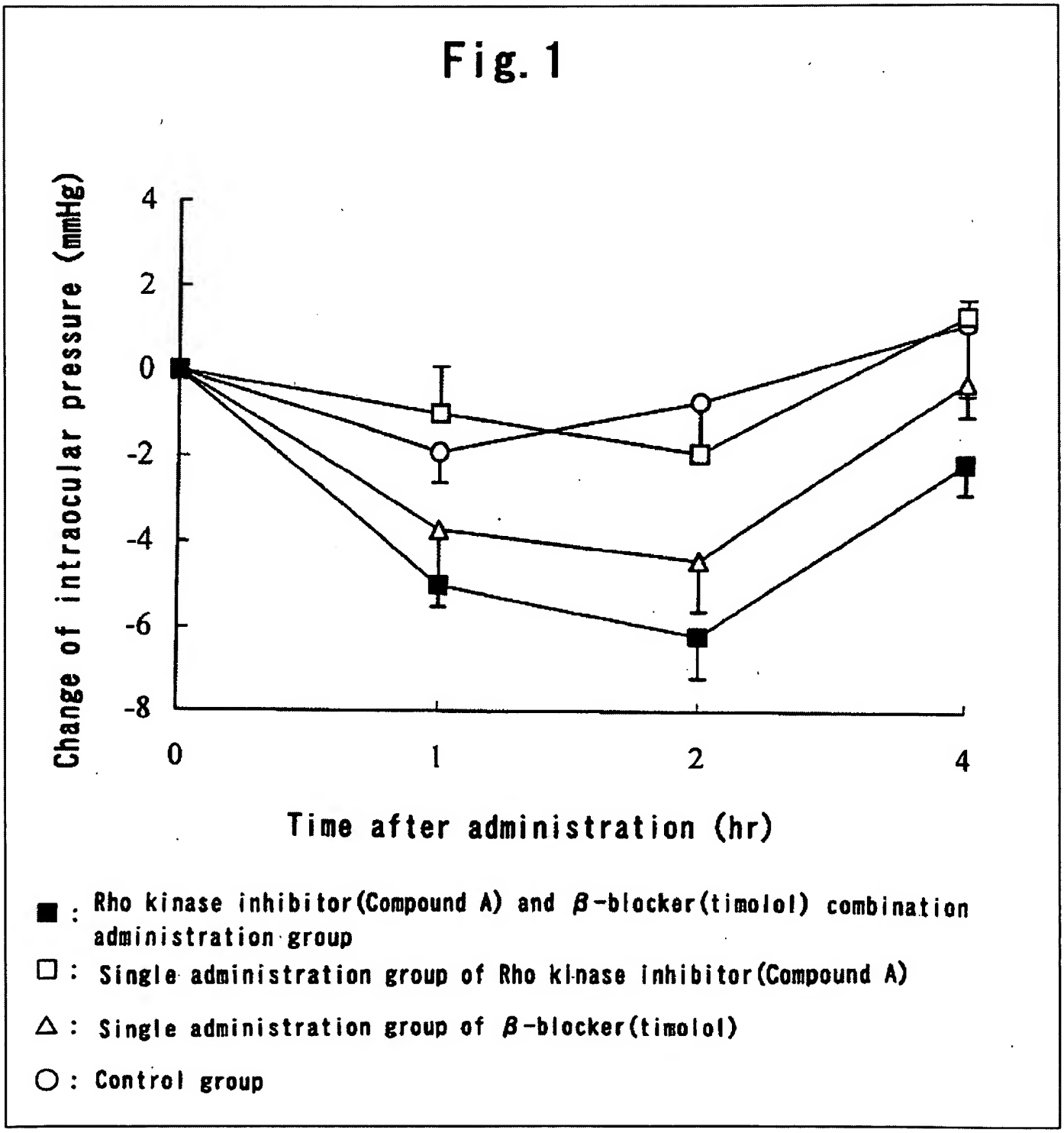


Table A IOP reduction from initial IOP after adminstration of HA1077 and timolol in combination as the difference from the control group

	Time after instillation			
	0hr	1hr	2hr	4hr
①Single administration group of HA1077	0	1.0 mmHg	1.2 mmHg	0.1 mmHg
②Single administration group of timolol	0	2.3 mmHg	1.9 mmHg	1.6 mmHg
③HA1077 and timolol combination administration group	0	3.2 mmHg	2.7 mmHg	0.9 mmHg
Theoretical additive IOP reduction (①+②)	0	3.3 mmHg	3.1 mmHg	1.7 mmHg

As apparent from the above Fig. A of the HITANO DECLARATION, the combination of HA1077 and timolol exhibited an additive effect 1 and 2 hours after instillation. However, 4 hours after instillation, HA1077 and timolol did not complement and/or enhance their actions with respect to each other, which means that persistence of the action is not improved by the combination of HA1077 and β-blocker. On the other hand, as shown in Fig. 1 of the present specification, the combination of Y-39983 and timolol complemented and/or enhanced their actions with respect to each other even 4 hours after instillation, which means that the presently claimed invention improves the persistence of the action.

Fig. 1 in applicants' application is as follows:



Further, the combination of HA1077 and timolol did not exhibit a synergistic effect at any time. The above Table A of the HATANO DECLARATION shows IOP reduction from an initial IOP after administration of HA1077 and timolol in combination as the difference from a control group. According to the above Table A of the HATANO DECLARATION, IOP reductions of a combination group after 1, 2 and 4 hours after instillation were 3.2 mmHg, 2.7 mmHg and 0.9 mmHg, respectively. It should be noted that the IOP reduction 4 hours after instillation was smaller than the theoretical additive IOP reduction, while the IOP reductions 1 and 2 hours after instillation were approximately equal to the theoretical additive IOP reductions (see the bottom row of the above Table A of the HATANO DECLARATION of the HATANO DECLARATION). Consequently, the above Table A of the HATANO DECLARATION supports the findings that the combination of HA1077 and timolol exhibits a partially additive effect, not a synergistic effect.

In contrast to the preceding paragraph, the combination of Y-39983 and timolol according to the presently claimed invention exhibited more than an additive effect (i.e., a synergistic effect) at each point in time as shown in Fig. 1 of the present specification. However, on page 4, lines 11 to 13 of the May 28, 2009 Office Action, the position was taken that applicants' Fig. 1 shows an additive result, and thus the synergistic effect of the presently claimed invention was not acknowledged. In view thereof, in the HATANO DECLARATION, the declarant calculated an IOP reduction from initial an IOP after administration of Y-39983 and timolol in combination as the difference from a control group. The results are shown in Table 1 of the HATANO DECLARATION, which is reproduced as follows.

Table 1 IOP reduction from initial IOP after administration of Y-39983 and timolol in combination as the difference from the control group

	Time after instillation			
	0hr	1hr	2hr	4hr
①Single administration group of Y-39983	0	-0.9 mmHg	1.2 mmHg	-0.2mmHg
②Single administration group of timolol	0	1.8 mmHg	3.7 mmHg	1.4 mmHg
③Y-39983 and timolol combination administration group	0	3.1 mmHg	5.5 mmHg	3.3 mmHg
Theoretical additive IOP reduction (①+②)	0	1.1 mmHg	4.9 mmHg	1.2 mmHg

According to the above Table 1 of the HATANO DECLARATION, IOP reductions of the combination group of Y-39983 and timolol after 1, 2 and 4 hours after instillation were 3.1 mmHg, 5.5 mmHg and 3.3 mmHg, respectively. It should be noted that the IOP reductions at any point in time were greater than the theoretical additive IOP reductions (see the bottom row of the above Table 1 of the HATANO DECLARATION). Consequently, Table 1 of the HATANO DECLARATION supports the finding that the combination of Y-39983 and timolol exhibits synergistic effect. This is an unpredictable result, considering that the combination of other Rho kinase inhibitors such as HA1077 and β-blocker exhibited merely a partially additive effect.

In conclusion, Y-39983 is more preferable to be combined with β-blocker than other Rho kinase inhibitors, such as HA1077. It

emphasized that there was heretofore a difficulty to find a preferable compound for combination use with a β-blocker among the many Rho kinase inhibitors, including more than two hundred Rho kinase inhibitors disclosed by Azuma et al. Thus, the success of the presently claimed invention could not have been reasonably expected.

Accordingly, it is respectfully submitted that the combination of the specific Rho kinase inhibitor recited in applicants' present claims and a beta-blocker, such as timolol, yield unpredictable results.

Withdrawal of the 35 USC 103 rejection based on Azuma et al. is therefore respectfully requested.

Reconsideration is requested. Allowance is solicited.

If the Examiner has any comments, questions, objections or recommendations, the Examiner is invited to telephone the undersigned at the telephone number given below for prompt action.

Respectfully submitted,

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Encl.: DECLARATION UNDER 37 CFR 1.132 of Masakazu HATANO dated July 21, 2009